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Multiple Neoplasms in an Irradiated Cohort: Pattern of Occurrence and Relationship to Thyroid Cancer Outcome

DAN MIHAILESCU, EILEEN SHORE-FREEDMAN, SONIA MUKANI, JAY LUBIN, ELAINE RON, AND ARTHUR B. SCHNEIDER

Section of Endocrinology and Metabolism (D.M., E.S.-F., S.M., A.B.S.), University of Illinois College of Medicine, Chicago, Illinois 60612; and Division of Cancer Epidemiology and Genetics (E.R., J.L.), National Cancer Institute, Bethesda, Maryland 20892

We have examined the pattern of four radiation-related neoplasms in a radiation-exposed cohort of 2795 patients. They had received conventional radiation treatments for benign conditions in the head and neck area when they were children. At the end of follow-up, 350 thyroid cancers, 108 benign and malignant salivary tumors, 87 neural tumors, and 70 cases of hyperparathyroidism had occurred. In 492 individuals (17.6% of the cohort), there were single tumors, and in 60 individuals (2.1%), there were multiple tumors. Because this was an apparent excess of multiple tumors, we tested the hypothesis that the excess arose, at least in part, from variation in radiation susceptibility in the cohort. To analyze this, we developed a method to account for differences in length of follow-up and known risk factors, such as age at radiation exposure, radiation dose, and gender. This analysis showed that the excess concordance of neoplasms could be explained by known risk factors, thereby suggesting that susceptibility factors did not play a role in the development of multiple tumors. Of the 350 thyroid cancers, 50 occurred in subjects with other radiation-related neoplasms. Therefore, we tested an additional hypothesis, that the presence of these other neoplasms was related to the clinical behavior of the thyroid cancer. Using thyroid cancer recurrence as the end point, we did not observe a relationship with the presence of other neoplasms. In summary, we demonstrated an excess of concordance of radiation-related neoplasms that could be explained by known risk factors, and we found that thyroid cancer behavior was not related to the occurrence of multiple tumors. (*J Clin Endocrinol Metab* 87: 3236–3241, 2002)

RADIATION TREATMENT DURING childhood for benign head and neck conditions is a well-known risk factor for the development of various tumors in the area of treatment (1, 2). In addition to benign and malignant thyroid neoplasms, radiation-exposed individuals are more likely to develop hyperparathyroidism, salivary gland tumors, and benign neural tumors of the head and neck (3–6). In a cohort of 2795 individuals receiving childhood radiotherapy as treatment for enlarged tonsils and adenoids, we reported that patients with salivary and neural tumors had an increased incidence of benign and malignant thyroid nodules (7). This apparent clustering was not explained by the known risk factors assessed at that time (dose, gender, and age at radiation exposure). Thus, we hypothesized that additional factors, such as radiation sensitivity, may have played a role in the development of these tumors. The evidence for genetic susceptibility factors, such as the ATM gene and DNA repair genes, contributing to the oncogenic effects of radiation, has been reviewed (8, 9).

In the 15 yr since we evaluated the occurrence of multiple primary tumors, there has been a substantial increase in the numbers of thyroid, salivary, and neural tumors in our radiation-exposed cohort (7). We have confirmed that hyperparathyroidism is associated with childhood irradiation (6) and have estimated organ-specific radiation doses (3). Furthermore, we have noted an increase in the number of individuals with multiple radiation-related tumors.

Because we have observed an apparent excess of multiple tumors, we tested the hypothesis that the excess arose, at least in part, from variation in radiation susceptibility in the cohort. A nonrandom distribution of tumors would provide evidence of the presence of radiation susceptibility factors. We tested the additional hypothesis that the occurrence of nonthyroid neoplasms helped predict the clinical behavior of the thyroid cancers.

The thyroid cancers occurring as a result of the Chernobyl accident emphasize the need to understand the behavior of these malignancies better (10, 11). There is evidence that Chernobyl-related cases presented with more advanced features and tended to be more aggressive than cases not associated with radiation (12–15). In the cohort described here, we also observed a high frequency of multicentricity and lymph node involvement but not more aggressive behavior (16, 17). Here, we consider the possibility that having another radiation-related tumor might be predictive of the behavior of a thyroid cancer.

Subjects and Methods

Population at risk

From 1939 through 1962, more than 5300 patients received radiation treatment for various benign conditions of the head and neck area at Michael Reese Hospital in Chicago. Criteria for including subjects in the cohort, the demographic characteristics of the study population, and the screening program were described previously (3). Most of the patients were treated for enlarged tonsils and adenoids. The final cohort includes 4296 patients who were treated for benign conditions with conventional external radiation and who were younger than 16 yr of age at the time

of first irradiation. In 2000 we concluded our most recent effort to contact everyone in the cohort to update their health information and provide them with information about the study findings. Individuals were contacted by mail and were asked to complete a study questionnaire and to give permission to obtain confirmatory information from their medical records. It was suggested to them that they continue to consult with their own physicians for follow-up. The 49 who between 1997 and 2000 elected to be evaluated at our institution were examined by a study physician and had a thyroid ultrasound. The present analysis is limited to 2795 patients (65.1% of the final cohort), excluding 1047 for lack of follow-up and 454 for insufficient information for dose estimation.

Head and neck tumor dosimetry and follow-up

Ascertainment of tumors was obtained directly from the patients and was confirmed by reviewing medical and pathology records. Thyroid cancer, hyperparathyroidism, salivary tumors (benign and malignant tumors of the parotid, submandibular, and sublingual glands), and nerve sheath tumors (schwannomas in the head and neck, vestibular schwannomas, and meningiomas) were included, *i.e.* head and neck tumors for which there is sufficient evidence to support an association with childhood irradiation. Hyperparathyroidism was defined as elevated calcium with an elevated PTH level or surgical correction of hypercalcemia by the removal of one or more parathyroid glands. Ten nonfunctioning parathyroid adenomas discovered as incidental findings during surgery for thyroid cancer were excluded from the analysis. For all tumors the date of diagnosis was considered to be the date of surgery. For hyperparathyroidism, the date of the first documented elevated calcium was used if surgery was not performed. If more than one tumor occurred in a given category, then only the first was included in the analysis.

The estimation of organ-specific doses for each individual is described elsewhere (3). The doses for the thyroid gland were used as estimates of the average dose to the parathyroids. For salivary tumors a combined weighted average dose was calculated from the dose estimates for each individual gland (4). Because of the variety of locations, dose estimates were not available for the neural and brain tumors, so dosimetry was excluded from the risk factor analysis for this category of tumors.

Follow-up time was defined as the time from the first x-ray treatment to the development of each tumor or, if no tumor occurred, until the most recent contact before November 1, 2000, which provided sufficient information to determine vital status.

Statistical analyses

To determine the expected number of cases of multiple tumors, without regard to the varying times of follow-up and varying risk factors, binomial probabilities were used. In other words, only the proportion of the cohort affected by each tumor was used for this calculation.

To include the varying times of follow-up and varying risk factors, we used the following method: For each tumor category, proportional hazards analysis (18) was performed to define significant risk factors and calculate the probabilities of developing a tumor, using the Epicure program (19). If a subject developed a tumor, they remained at risk for the other tumors until the end of follow-up. The regression coefficient and upper and lower confidence bounds were determined for each potential risk factor (covariate) analyzed. The factor was considered to contribute significantly to the relative risk for developing the tumor if the confidence intervals did not include one. The individual factors selected in this way were combined to form the final model. From this analysis a baseline cumulative hazard value, with covariates set to zero, was calculated and assigned to each individual. A corrected hazard was then calculated based on the individuals' actual covariates. This corrected hazard is the expected value for a given tumor for a given individual. The sum of the expected values for the whole cohort is equal to the number of tumors actually observed (thyroid = 350, salivary = 108, neural = 87, hyperparathyroidism = 70).

The statistic used to determine whether there is a difference between a random distribution of the tumors in the cohort and the actual distribution is based on the differences between the observed and expected values. Each individual has an expected value for each tumor, and having or not having a particular tumor deviates from the expected. For each subject their "deviation from expected" is the sum of the differences between the observed (0 = absent, 1 = present) and expected values for each tumor. The absolute value of this sum is their concordance score. It is a concordance score because values are higher when multiple tumors occur in a single subject and when no tumors occur, which also is a deviation from expected. Thus, the concordance score has the following important properties: It takes into account the magnitudes of all of the significant risk factors, it combines the presence or absence of all tumors, and it increases as the sum of the deviations from expected increase.

The overall concordance for the entire cohort was characterized by the sum of the individual concordance scores. This is referred to as the population concordance index; the more concordance in the population, the higher this number. The principal hypothesis was tested by determining whether the observed population concordance index was higher than expected. Expected was taken as the 95% bounds of population concordance indices generated by randomly permutating the tumors in the population. In other words, new hypothetical populations were formed with the same characteristics as the observed one, except that the pattern of tumors among individuals was randomized. Specifically, for each tumor the deviations from expected were randomized. In this way, the effect of concordance was isolated and tested specifically. The randomization was repeated 1000 times, and a population concordance index was calculated for each one. These were compared with the index observed in the cohort.

To test whether in individuals with thyroid cancer and another tumor there was a preferential temporal ordering of the neoplasms, it was necessary to take into account the individual time trends for each tumor. Specifically, in the entire cohort, thyroid cancers occurred earlier than the other tumors. The order of the observed tumor pairs (thyroid cancer and another tumor) was compared with pairs obtained by randomly selecting from the entire population.

The characteristics of different groups were compared using chi-square and *t* tests (6.0, NCSS, Kaysville, UT). SigmaPlot 4.0 (SPSS, Inc., Chicago, IL) was used for the Kaplan-Meier plots.

Results

During the study follow-up, 350 thyroid cancers, 108 benign and malignant salivary tumors, 87 neural tumors, and 70 cases of hyperparathyroidism were diagnosed among the 2795 cohort members (Table 1). Most of the subjects (80.3%) had no tumors, 17.6% (492 individuals) developed one tumor (referred to as single tumors), and 2.1% (60 patients) developed two or more tumors (referred to as multiple tumors).

The characteristics of the subjects who developed multiple tumors were compared with those of the subjects who developed a single or no tumor (Table 2). The majority of the

TABLE 1. Types and distribution of head and neck tumors in the cohort

Head and neck tumors (n = 615)	
Thyroid cancer	350
Salivary tumors	108
Neural tumors	87
Hyperparathyroidism	70
Subjects with single tumors (n = 492)	
Thyroid cancer	300
Salivary tumors	79
Neural tumors	67
Hyperparathyroidism	46
Subjects with multiple tumors (n = 60)	
Thyroid + salivary	18
Thyroid + parathyroid	17
Thyroid + neural	12
Salivary + parathyroid	4
Salivary + neural	6
Thyroid + salivary + parathyroid	1
Thyroid + neural + parathyroid	2

individuals in both groups were male (70% and 59.6%, respectively). The subjects in the multiple tumor group were significantly younger at the time of first irradiation and were exposed to higher radiation doses to the thyroid than subjects in the single and no tumor group.

An initial inspection of the pattern of the tumors in the cohort indicated more concordance than expected (Table 3). Using binomial probabilities, there appeared to be an excess of subjects with three tumors (3 *vs.* 1.09 expected), two tumors (57 *vs.* 38.18 expected), and no tumors (2243 *vs.* 2220 expected) and a deficit of subjects with one tumor (492 *vs.* 535.3 expected). Inspecting all possible tumor combinations shows that the association between thyroid cancer and hyperparathyroidism is most important. Specifically, 19 individuals had both thyroid cancer and hyperparathyroidism with only 8.73 cases expected (Table 3). However, binomial probabilities do not take into account the varying length of follow-up and the different risk factors for each member of the cohort.

TABLE 2. Comparison of the characteristics of subjects with multiple tumors, single tumors, and no tumors

	Multiple tumors (n = 60)	Single tumors (n = 492)	No tumors (n = 2243)
Males (%)	70	51.8	61.3
Age at Rx (yr)[a]	3.62 ± 2.23	4.12 ± 2.97	4.33 ± 3.08
Dose (cGy)[b]	76.55 ± 51.31	65.29 ± 42.32	56.66 ± 31.34

Values are the mean ± SD.
[a] $P = 0.02$ and [b] $P = 0.008$ for multiple tumors *vs.* single and no tumors combined.

Risk factors analysis

Previous reports demonstrated that the dose of radiation, younger age at treatment, and female sex were significant risk factors for the development of various head and neck tumors. These risk factors were analyzed again for the cohort included in this study. The relative risk and the confidence intervals for the significant risk factors are given in Table 4. This analysis supported the previous observations that radiation dose is a significant risk factor for thyroid cancer, salivary tumors (benign and malignant combined), and hyperparathyroidism. Again, younger age at treatment and female sex were found to be significant risk factors for developing thyroid cancer. Because of the different locations of

TABLE 3. Estimates of multiple tumor occurrences excluding risk factors

Neoplasm Groupings	No. of Neoplasms	No. of Subjects		χ^2	P
		Observed	Expected		
Thyroid-salivary-parathyroid	0	2243	2220.46	16.267	0.003
	1	492	535.27		
Neural	2	57	38.18		
	3	3	1.09		
	4	0	0.00		
Thyroid-salivary-parathyroid	0	2310	2291.49	16.354	0.001
	1	443	479.11		
	2	41	24.06		
	3	1	0.34		
Thyroid-salivary-neural	0	2289	2277.39	7.375	0.061
	1	467	490.62		
	2	39	26.57		
	3	0	0.42		
Thyroid-parathyroid-neural	0	2322	2310.57	14.716	0.002
	1	441	463.25		
	2	30	20.92		
	3	2	0.27		
Salivary-parathyroid-neural	0	2543	2537.66	3.654	0.301
	1	239	249.24		
	2	13	8.019		
	3	0	0.084		
Thyroid-salivary	0	2356	2350.32	2.348	0.309
	1	420	430.99		
	2	19	13.70		
Thyroid-parathyroid	0	2389	2384.48	12.615	0.0018
	1	387	401.78		
	2	19	8.73		
Thyroid-neural	0	2368	2369.88	0.887	0.642
	1	413	414.22		
	2	14	10.90		
Salivary-parathyroid	0	2610	2618.85	2.241	0.326
	1	180	173.43		
	2	5	2.73		
Salivary-neural	0	2589	2602.70	2.713	0.258
	1	200	188.94		
	2	6	3.35		
Parathyroid-neural	0	2622	2640.65	2.41	0.291
	1	171	152.19		
	2	2	2.17		

TABLE 4. Risk factors for the different head and neck tumors

	Thyroid	Salivary	Parathyroid	Neural
Age at Rx (yr)	0.93 (0.89–0.97)	1.01 (0.96–1.08)	0.96 (0.89–1.04)	0.97 (0.90–1.04)
Sex (M/F)	0.75 (0.60–0.92)	0.96 (0.65–1.41)	0.86 (0.54–1.38)	1.21 (0.78–1.87)
Dose (cGy)	1.003 (1.001–1.005)	1.38 (1.01–1.89)	1.004 (1.00–1.007)	[a]

Factors used in the final model were age at treatment, sex and dose for thyroid cancer and dose for salivary tumors and parathyroid tumors. Relative risks and 95% upper and lower confidence intervals are given for each factor.

[a] Dosimetry was not available for the neural tumor group. For this group there is no single dose estimate because the tumors occurred at multiple sites in the head and neck.

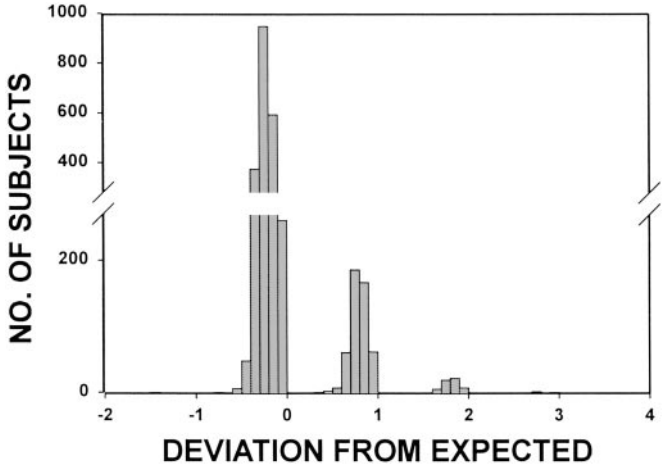

FIG. 1. Distribution of the individual subjects' concordance indices. Sums of the observed (zero or one) minus expected (calculated from the cumulative hazard) values [Σ;(O-E)] over the four tumor types (thyroid, salivary, parathyroid, and neural), shown as a frequency histogram for the 2795 subjects in the study. The sum of the values shown is, by definition, zero. The sum of the absolute values is 1001.40.

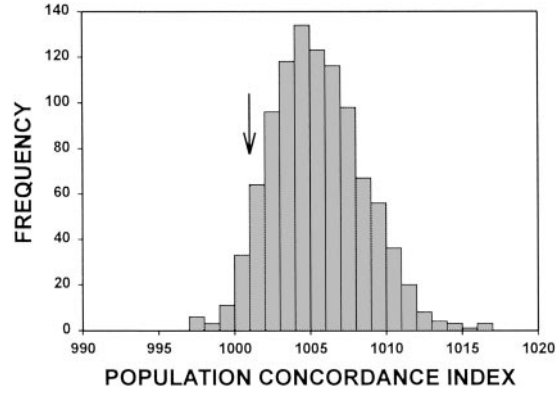

FIG. 2. Comparison of the observed with the expected population concordance index. The observed population concordance index (1001.4), *i.e.* the sum of the absolute values of the Σ;(O-E)s shown in Fig. 1 is indicated by the *vertical line.* The population concordance indices obtained from 1000 random permutations are shown as a frequency histogram. Ninety-five percent of the values shown fell in the range 1000.1–1011.7.

the neural and brain tumors, there is no single dose that could be included in the analysis. Neither the patient's gender nor age at radiation treatment was found to be a significant risk factor for salivary, parathyroid, and neural tumors.

Distribution of different head and neck tumors

The distribution of the 2795 concordance scores for the individuals in the cohort is shown in Fig. 1. The values cluster near the integer that corresponds to the number of tumors that occurred, and the scatter represents the effect of taking the length of follow-up and risk factors into account. By definition, the sum of the values shown is zero. The sum of the absolute values, the population concordance index, is 1001.4. By comparison, the highest theoretical value for the population concordance index is 1156.39 (for complete overlap of the tumors), and the lowest theoretical value is 864.6 (for the least possible overlap).

The population concordance indices obtained from the 1000 random permutations of the cohort are shown in Fig. 2. The distribution of the values is approximately normal with a mean of 1005.48 (±3.02 SD). The observed population concordance index of 1001.4 was within the 95% bounds of the randomly generated population (1000.1–1011.7). Thus, the apparent excess of concordance seen in Table 3 is accounted for by variations in length of follow-up time and the other identified risk factors. Because the relationship between thyroid cancer and hyperparathyroidism appeared to be strongest (Table 3), the same approach was applied but only for these two neoplasms. The population concordance index was 749.25, compared with the randomly generated population, which had a mean of 751.01 and a 95% confidence range of 748.25–753.77.

Thyroid cancer characteristics as a function of accompanying head and neck tumors

Thyroid cancer was the most common tumor encountered in the cohort, representing 56.9% (350 of 615) of all of the tumors. Of the 350 thyroid cancers, 50 occurred in subjects with other radiation-related neoplasms. The characteristics of the thyroid cancers in subjects with and without other tumors are shown in Table 5. More males, younger age at exposure, and higher thyroid doses characterized the group with thyroid cancer and other tumors. The only difference in the presenting characteristics of the thyroid cancers was that lymph node involvement was more frequent in the group without other tumors.

We analyzed the chronological distribution of various tumors. Thyroid cancer was the first tumor detected in 31 (73.8%) of the multiple-tumor patients, which included thyroid cancer, whereas another tumor (salivary, neural, or parathyroid) was the presenting neoplasm in 11 (26.2%) patients (Table 6). The data from the entire cohort were used to calculate the expected order for the patients with thyroid cancer and another tumor. Six subjects who had the same date of onset for two tumors were excluded from this calculation. There was no evidence that the order of the neo-

TABLE 5. Characteristics of thyroid cancers in two groups: thyroid cancer alone and thyroid cancer in subjects with other head and neck tumors

	Thyroid cancer alone	Thyroid cancer with other tumors
Demographic characteristics		
No. of subjects	300	50
Male (%)[a]	50.7	66.0
Age at radiation treatment (yr)[a]	3.8 ± 2.7	3.4 ± 1.9
Thyroid dose (cGy)[b]	63.1 ± 36.8	77.1 ± 54.7
Age at thyroid cancer (yr)	31.2 ± 8.9	33.1 ± 12.3
Pathological characteristics		
Size (mm)	12.3 ± 10.1	13.4 ± 12.9
Lymph node involvement (%)[a]	33.6	19.1
Unilateral (%)	72.7	72.3
Invasion into soft tissue (%)	9.89	10.2
Vascular invasion (%)	12.1	10.4
Multifocal (%)	54.5	47.8
Histology (% papillary)	90.9	87.8
Treatment characteristics		
Recurrence (%)	15.3	14.0
Radioactive iodine for completion (%)	32.7	22.0

The following data were unavailable: bilaterality in 22 patients with single and 3 patients with multiple tumors, multicentricity in 20 patients with single and 4 patients with multiple tumors, invasiveness in 17 patients with single and 1 patient with multiple tumors, lymph node involvement in 17 patients with single and 3 patients with multiple tumors, vascular invasion in 19 patients with single and 2 patients with multiple tumors.

[a] $P < 0.05$ by t test or χ^2 analysis.

[b] $P < 0.001$ by t test.

TABLE 6. First tumor to occur in subjects who developed thyroid cancer and another asynchronous neoplasm

First tumor	Observed	Expected
Thyroid cancer	31	29.5
All others	11	12.5
Total	42	42

$P > 0.1$.

plasms in the subjects affected with more than one was different from the expected.

The overall frequency of recurrence was the same for the thyroid cancers with and without other tumors (14.0% *vs.* 15.3%). This was confirmed by comparing the Kaplan-Meier plots for the two groups and finding no difference in recurrence-free survival through 30 yr of follow-up (Fig. 3). The apparent divergence after 30 yr is based on only two cases, too few to be meaningful.

Discussion

The first goal of the present study was to examine the pattern of radiation-related neoplasms in the Michael Reese Hospital cohort for evidence of excess concordance of tumors in individuals. A pattern with excess concordance would be consistent with a spectrum of radiation susceptibility, with susceptible individuals tending to have multiple tumors and resistant individuals tending to have none. We adapted a method previously devised by us (20) to incorporate length of follow-up and other risk factors into the analysis, and the current analysis is considerably expanded and refined.

Fifteen years have elapsed since our analysis of multiple tumors (7). The additional follow-up time has resulted in an

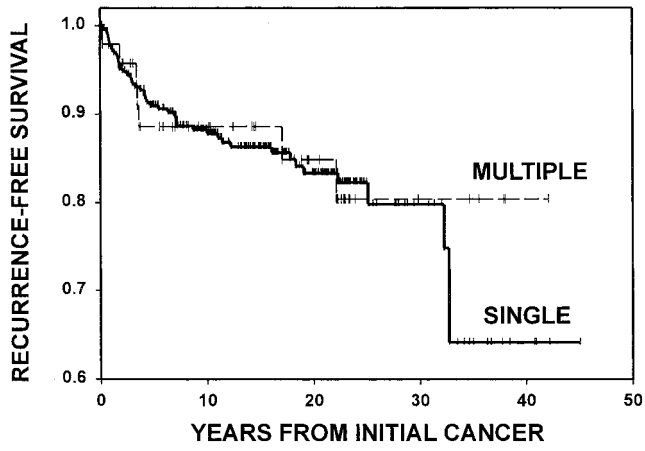

FIG. 3. Recurrence-free survival by Kaplan-Meier analysis in subjects with thyroid cancer alone and thyroid cancer and one or more additional tumors.

increased number of tumors; the inclusion of hyperparathyroidism as a radiation-related tumor (6); individual dose estimates for the thyroid, parathyroid, and salivary glands (dose estimates for the neural tumors are in progress but are complicated by the fact that the neural tumors occurred in a wide range of sites); and, finally, better statistical methods. Benign thyroid nodules are not included in the current analysis because of the increasingly widespread use of thyroid ultrasound in the intervening period. Ultrasound examinations of a sample of this cohort suggest that about 90% of the cohort could be classified as having nodular thyroid disease (17). Such a high proportion would make including all of them virtually meaningless. Even selecting an arbitrary size criterion would not eliminate a strong bias because nearly half of larger nodules detected by ultrasound were not found by physical examination.

Although the proportion of multiple tumors was higher than expected in our current study, the excess could be accounted for by variations in length of follow-up and risk factors. No additional concordance was present to suggest increased susceptibility in some members of the cohort. This, of course, does not exclude the possibility that radiation susceptibility factors do exist (8). A very few subjects with very high susceptibility would go unnoticed in a large cohort. Also, subtle susceptibility factors may be present but with insufficient effect to be detected by the current approach. Because there is excess concordance, whether because of identifiable risk factors or due to variable radiation susceptibility, it remains good practice, when one radiation-related neoplasm is detected, to look carefully for others.

The second goal of the present study was to determine whether there were any differences in the presentation or behavior of the thyroid cancers in patients with other radiation-related neoplasms, compared with patients who had thyroid cancer alone. The behavior, as measured by recurrence, was essentially identical for the two groups, and the pathological features, with the exception of more frequent lymph node involvement in the patients with thyroid cancer alone, did not differ. This finding is in contrast to the differences seen between radiation-related thyroid cancers and

sporadic thyroid cancers. Radiation-related cancers occur at younger ages, have more frequent lymph node involvement, and are more often multicentric. However, when these factors are taken into account, the behavior appears to be the same (16).

In summary, the management of radiation-related thyroid cancer should not be influenced by the presence of other radiation-related neoplasms (2). Although the presence of one radiation-related neoplasm should signal the need to look for others, the increased concordance that is observed appears to be due to identifiable risk factors and not to variation in radiation susceptibility.

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Address all correspondence and requests for reprints to: Arthur B. Schneider, M.D., Ph.D., University of Illinois at Chicago, Section of Endocrinology and Metabolism, 1819 West Polk Street, MC 640, Chicago, Illinois 60612. E-mail: abschnei@uic.edu.

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